Effect of Sitagliptin on Kidney Function and Respective Cardiovascular Outcomes in Type 2 Diabetes: Outcomes from TECOS

Running Title: Kidney Function and CV Outcomes With Sitagliptin

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Counts:

Abstract: 249 words (Max 250); Text: 2,437 words (Max 4,000)

Tables: 3; Figures: 1 (max 4 tables/figures); References: 27 (Max 40)

Abstract

OBJECTIVE

To evaluate chronic kidney disease (CKD) and cardiovascular outcomes in TECOS participants with type 2 diabetes and cardiovascular disease treated with sitagliptin, a dipeptidyl peptidase-4 inhibitor (DPP-4i), according to baseline estimated glomerular filtration rate (eGFR).

RESEARCH DESIGN AND METHODS

We used data from 14,671 TECOS participants assigned double-blind to receive sitagliptin or placebo added to existing therapy, whilst aiming for glycemic equipoise between groups. Cardiovascular and CKD outcomes were evaluated over median of 3 years, with participants categorized at baseline into eGFR stages 1, 2, 3a and 3b (≥90, 60-89, 45-59 or 30-44 ml/min/1.73m^2, respectively).

RESULTS

Participants with eGFR stage 3b were older, more often female and had longer diabetes duration. Four-point MACE rates increased with lower baseline eGFR (3.52, 3.55, 5.74 and 7.34 events *per* 100 patient-years for stages 1-3b, respectively. Corresponding adjusted hazard ratios (95% CI) for stages 2, 3a and 3b versus stage 1 were 0.93 (0.82–1.06), 1.28 (1.10–1.49) and 1.39 (1.13–1.72), respectively. Sitagliptin was not associated with cardiovascular outcomes for any eGFR stage (interaction *P* values all >0.44). Kidney function declined at the same rate in both treatment groups, with a marginally lower but constant eGFR difference (−1.3 ml/min/1.73m^2) in those assigned to sitagliptin. Treatment differences in these eGFR values remained after adjustment for region, baseline eGFR, baseline HbA_{1c}, time of assessment and within-study HbA_{1c} levels.

CONCLUSIONS

Impaired kidney function is associated with worse cardiovascular outcomes. Sitagliptin has no clinically significant impact on cardiovascular or CKD outcomes, irrespective of baseline eGFR. (TECOS ClinicalTrials.gov number, NCT00790205)

Introduction

Patients with type 2 diabetes mellitus are at high risk for macrovascular and microvascular complications [1], with type 2 diabetes being a key risk factor for the development of chronic kidney disease (CKD). CKD further increases the risk of adverse cardiovascular (CV) outcomes, especially in patients with known CV disease [2–5], and both microalbuminuria and macroalbuminuria are associated independently with an increased risk of CV events [6]. Accordingly, the potential impact of type 2 diabetes therapies on CV and CKD outcomes is a major consideration in the long-term management strategy of the disease. Intensified glucose control and multiple CV risk factor therapies can reduce CV risk in general, and diabetic nephropathy in particular [7,8], but there is a paucity of data on the effectiveness of specific type 2 diabetes treatment regimens with regard to these two outcomes.

The Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) [9] showed that adding sitagliptin to usual care, compared with placebo, in patients with type 2 diabetes and established CV disease did not impact on the risk of major CV outcomes, hospitalization for heart failure or adverse events in general. The aim of the present *post hoc* analysis was to evaluate CV and CKD outcomes in TECOS participants with type 2 diabetes and CV disease when treated with sitagliptin, a dipeptidyl peptidase-4 inhibitor (DPP-4i), according to their baseline estimated glomerular filtration (eGFR) stage.

Research Design and Methods

The rationale and design of TECOS [10], as well as its primary outcomes and safety measures [9], have been reported. Briefly, 14,735 participants from 38 countries were enrolled between December 2008 and July 2012. Eligible participants were ≥50 years old with type 2 diabetes,

established atherosclerotic CV disease, and HbA_{1c} values 6.5–8.0% (48–64 mmol/mol), and on stable-dose mono- or dual-combination therapy with metformin, pioglitazone, or sulfonylurea, or insulin with or without metformin. Patients with eGFR values <30 ml/min/1.73m^2 were excluded.

Participants were randomized double-blind to sitagliptin 100 mg/day or placebo, with a lower dose of 50 mg/day for those with eGFR values 30 to 50 ml/min/1.73m^2. During the study, sitagliptin doses were adjusted, based on at least annual eGFR values, to 50 mg/day if 30 to 50 ml/min/1.73m^2 and to 25 mg/day if below 30 ml/min/1.73m^2. If a sustained eGFR recovery occurred, sitagliptin doses could also be up-titrated.

Treatment for type 2 diabetes and its comorbidities was provided by usual care providers, based on local guidelines. Any other glucose-lowering agent could be added, except for a GLP-1 receptor agonist or an open-label DPP-4i, with rosiglitazone use discouraged.

The study was managed and all data adjudicated and analyzed by academic partners (Duke Clinical Research Institute [DCRI] and the University of Oxford Diabetes Trials Unit). The database was held at and independently verified by the DCRI.

Ascertainment of CV Outcomes

An independent clinical events committee (CEC), blinded to treatment allocation, adjudicated all events of death, myocardial infarction (MI), stroke, hospitalization for unstable angina and hospitalization for heart failure [10]. The CEC, which was independent of both the sponsor and the TECOS Executive Committee, remained blinded to study treatment assignment. The primary CV composite outcome was a 4-point major adverse CV event (MACE), defined as time to CV death, nonfatal MI, nonfatal stroke or hospitalization for unstable angina.

Ascertainment of Kidney Function

Kidney function during the trial was assessed by annual usual care measurements of eGFR, calculated using the Modification of Diet in Renal Disease Study equation [11]. For a subset of participants, usual care urinary albumin-to-creatinine ratio (UACR) measurements were also available.

Statistical Analysis

Participants were categorized at baseline into eGFR stages 1, 2, 3a and 3b (≥90, 60-89, 45-59 or 30-44 ml/min/1.73m2, respectively) [12], and into three UACR groups according to their baseline values (normoalbuminuria: <30 mg/g, microalbuminuria: 30-300 mg/g and macroalbuminuria: >300 mg/g). Baseline characteristics for the intention-to-treat (ITT) population were summarized as mean (±1 standard deviation) or median (25^{th}, 75^{th} percentile) for quantitative data, and as percentages for categorical data.

Separate Kaplan-Meier plots for the primary 4-point MACE outcome were created for each eGFR stage, split by assigned study treatment or by HbA_{1c} level above or below the median. Possible associations between CV outcomes and the CKD stage or the UACR category were evaluated using Cox proportional hazards regression models, with region included as a stratification variable and adjustment covariates taken from models developed previously for the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial [13-15]. Less than 4% of the adjustment variables had missing values apart from low-density lipoprotein cholesterol (24%), hemoglobin (34%) and UACR (65%). For modeling purposes, missing baseline data were imputed using SAS PROC MI (SAS Institute; Cary, NC,

USA). Cardiovascular outcome rates are presented as total number of events, and as events *per* 100 patient-years of follow-up. Adjusted hazard ratios and 95% confidence intervals are presented for each of eGFR stages 2-3b, with stage 1 as the reference group. Models were repeated with the addition of the treatment-by-eGFR interaction.

Kidney-related outcomes included changes from baseline in eGFR and UACR, as specified in the TECOS protocol and statistical analysis plan [9]. Repeated measures analysis of variance was used to test for between treatment group eGFR and UACR differences over 4 years, with the overall difference summarized as the least-squares mean difference and 95% confidence interval. Overall least-squares mean differences are presented for all patients and separately for each eGFR stage, with *P* values for the treatment group by eGFR stage interaction. Models were adjusted for region, baseline eGFR or UACR, and for study visit. The model for the association between treatment and eGFR changes over 4 years was also performed with adjustment for baseline HbA_{1c} and change in HbA_{1c} from baseline to each visit.

Data were analyzed with SAS version 9.4. *P* values <0.05 were considered statistically significant, with no adjustments made for multiple testing.

Results

Study Patients

The ITT population comprised 14,671 participants with a median follow-up of 3.0 years (2.3 to 3.8, maximum 5.7). Overall, 95.1% and 94.1% of participants allocated to sitagliptin and placebo, respectively, completed the study, with 26.1% and 27.5%, respectively, discontinuing study medication prematurely. Vital status was determined at study end for 97.5% of participants.

Baseline eGFR measurements were available for 14,525 of the 14,671 ITT participants, categorized as stage 1 (3,325, 22.9%), stage 2 (7,879, 54.2%), stage 3a (2,538, 17.5%) and stage 3b (783, 5.4%). The 146 not included comprised 143 with missing baseline eGFR values and 3 with eGFR values <30 ml/min/1.73m^2 that did not meet the TECOS eGFR exclusion criterion. Participant baseline characteristics by eGFR stage are presented in Supplemental Table ST1. Participants with stage 3b kidney disease were older, more frequently women, had a longer duration of diabetes, tended to have a higher UACR, more likely to have a history of heart failure and to be receiving insulin or diuretics, but less likely to be current smokers or receiving metformin. For eGFR outcome analyses, a subset of 13,604 participants with at least one post-baseline eGFR measurement was used (93% of 14,671).

Baseline UACR measurements were available for 5,148 of the 14,671 ITT participants, categorized as having normoalbuminuria (3,701, 71.9%), microalbuminuria (1,200, 23.3%) or macroalbuminuria (247, 4.8%). For UACR outcome analyses, a subset of 3,832 (26% of 14,671) participants with baseline UACR and eGFR measurements and at least one post-baseline UACR measurement was used.

Cardiovascular Outcomes

Table 1 shows CV outcomes by baseline eGFR stage. Rates for the primary 4-point MACE outcome increased with lower eGFR values, being 3.52, 3.55, 5.74 and 7.34 events *per* 100 patient-years for stages 1-3b, respectively. The corresponding adjusted hazard ratios (95% CI), with stage 1 as the reference stage, were 0.93 (0.82–1.06), 1.28 (1.10–1.49) and 1.39 (1.13–1.72) respectively. Rates increased similarly for the secondary 3-point MACE outcome (CV death, nonfatal MI or nonfatal stroke) and all other secondary outcomes, except for hospitalization for

unstable angina. There were no significant interactions (all p>0.44) between continuous eGFR measurements and randomized treatment allocation (Supplemental Table ST2).

Sitagliptin did not impact on the primary 4-point MACE outcome irrespective of baseline eGFR stage, as shown by Kaplan-Meier curves (Supplemental Figure SF1). Lower event rates were seen in those who had within-study HbA_{1c} values below the median, compared with those with HbA_{1c} values greater than the median (Supplemental Figure SF2).

Table 2 shows the CV outcomes by baseline UACR category. Cardiovascular outcomes worsened with increasing albuminuria, except for 4-point MACE, MI, stroke and hospitalization for unstable angina. The modelled impact of continuous baseline eGFR and UACR values on the 4-point MACE primary outcome are shown in Supplemental Figure SF3. Rates increase substantially with eGFR values <60 ml/min/1.73m^2 and with UACR values >30 mg/g.

Kidney Outcomes

The mean eGFR reduction over 4 years from baseline was greater in the sitagliptin than in the placebo group (-4.0±18.4 vs. -2.8±18.3 ml/min/1.73m^2). The mean eGFR value was marginally lower in the sitagliptin group at the first post-randomization visit and remained consistently lower thereafter (Figure 1A), with an overall estimated least-squares mean difference of -1.34 ml/min/1.73m^2 (95% CI, -1.76 to -0.91; *P*<0.001) (Table 3). The uniform eGFR decline over time and the 4-year between treatment group differences were similar for each eGFR stage, with no significant interactions of treatment effect by eGFR stage (Table 3, Supplemental Figure SF4). The slight eGFR difference between treatment groups remained after adjusting for time from randomization when eGFR was measured, baseline eGFR, baseline HbA_{1c}, HbA_{1c} change

over time and region (Supplemental Table ST3), with an estimated overall mean difference of -1.43 ml/min/1.73m^2 (95% CI -1.88 to -0.98, p<0.0001).

In the subset of participants with UACR data, the median value was marginally and consistently lower in the sitagliptin compared with the placebo group (Figure 1B), with an estimated overall mean difference of -0.18 mg/g (95% CI, -0.35 to -0.02, p=0.031) (Table 3). The 4-year UACR between treatment group differences were similar for each eGFR stage, with no significant interactions of treatment effect by eGFR stage (Table 3).

Discussion

TECOS was a global clinical trial demonstrating that the addition of sitagliptin to usual care in patients with type 2 diabetes and established CV disease did not affect rates of major atherosclerotic CV events in a setting of glycemic equipoise. This study shows that, although CV events are more frequent in patients with lower levels of kidney function, there is no interaction with the addition of sitagliptin. Kidney function declined at the same rate in both the sitagliptin and placebo groups, but with a slightly lower and constant eGFR difference in those assigned to sitagliptin.

CV Outcomes

The primary 4-point MACE outcome rate was progressively higher in participants with lower eGFR levels, as was the 3-point MACE outcome rate in those with an increased UACR. These data confirm earlier observational studies in which both eGFR and albuminuria have been shown to be independently associated with increased mortality and morbidity [3]. Interestingly, the rise in the rate of the primary 4-point MACE outcome starts with a UACR as low as 30 mg/g,

emphasizing albuminuria as a strong predictor of risk, as shown previously by Matsushita *et al.* [16]. As would be expected, TECOS participants with reduced baseline kidney function were less likely to be taking metformin and more often on insulin therapy, but with no difference in rates of sulfonylurea use. Despite the varying glucose-lowering strategies, sitagliptin had no effect on the primary 4-point MACE outcome at any eGFR or UACR level, and thus appears to be safe with respect to CV outcomes in patients with decreased kidney function.

CKD Outcomes

Although the mean eGFR during the trial was marginally lower in the sitagliptin compared with the placebo group, even when adjusted for glycemic control, the rate of eGFR decline was the same. Mean UACR values were also marginally lower with sitagliptin than with placebo in the 26% of TECOS participants with these data available. It is uncertain whether these small offsets in eGFR and UACR would have any long-term clinical implications. Similar observations of a decrease in UACR have been made in *post hoc* pooled analyses of phase 3 DPP-4i studies using linagliptin [17]. Animal studies in streptozotocin-induced diabetic rats found DPP-4i treatment improved albuminuria, with similar improvements in creatinine clearance [18]. Although microalbuminuria rates can be reduced by improving glucose control [19], the minimal effects of sitagliptin on eGFR and UACR appear to be unrelated to its glucose-lowering effects, since they are not explained by baseline HbA_{1c} or HbA_{1c} changes during the trial. While the small eGFR offset occurs early, and is stable over time for all GFR categories, there is no evidence of progression and appears to be similar for other DPP4 inhibitors as well [20].

TECOS did not show a clinically relevant improvement of kidney outcomes in patients treated with sitagliptin. Microvascular complication rates are related to HbA_{1c} levels [21], and

can be reduced with improved glycemic control [22,23], but in TECOS there was only a small difference in HbA_{1c} levels between treatment groups as the study aimed to achieve glycemic equipoise in order to minimize possible glycemic confounding effects on the outcomes of interest. Decline of kidney function in diabetes is often but not always preceded by glomerular hyperfiltration, possibly as early as the stage of impaired fasting glucose [24]. Glomerular hyperfiltration is associated with high glucose levels and changes in tubuloglomerular feedback related to alterations in vasoactive mediators, such as nitric oxide and cyclooxygenase-2 derived prostanoids, resulting in glomerular hypertension. These changes contribute to the inflammatory nature of diabetes that affects the vasculature and is directly associated with the genesis of microalbuminuria. Ultimately, in a subgroup of people, there is a decline in kidney function with some individuals progressing to end-stage renal disease [25,26]. Early studies suggested microalbuminuria was a predictor of faster declines of kidney function, but over the past decade the data clearly indicate it is a marker of increased CV disease risk in various pathophysiologic conditions, such as diabetes [26,27].

The strength of the present study was the large number of patients studied in a double-blind prospective manner. Limitations include the fact that follow-up may be relatively short for evaluating risk of development of diabetic nephropathy, especially in view of the biphasic change in GFR with initial hyperfiltration followed by a decrease in GFR. Furthermore, no differences were taken into account for eGFR stage 1 and CKD stage 1 in which microalbuminuria must be present and which may be a somewhat different class of patients.

In conclusion, reduced eGFR and increased UACR were associated with significantly increased risk of CV events, but we observed no clinically significant effect of sitagliptin

treatment on CV outcomes or CKD progression in patients with different CKD categories at baseline.

Acknowledgments. The authors wish to thank the investigators, staff, and participants in the TECOS trial without whose efforts and collaboration this work would not have been possible. We thank the following academic partners and contract research organizations for their assistance: Parexel International, Jubilant Clinsys, Clinogent, Canadian VIGOUR Centre, Green Lane Coordinating Centre, and South Australian Health and Medical Research Institute.

Funding. Funded by Merck Sharp & Dohme, a subsidiary of Merck & Co., Inc.

Duality of Interests. J.H.C. has received personal fees from Merck, and Eli Lilly, and AstraZeneca. **G.L.B.** reports serving as consultant for Merck, Bayer, Boehringer-Ingelheim, AbbVie, Janssen, NxStage, Astra Zeneca, Sanofi. **S.S.E.** is an employee of Merck Sharp & Dohme., a subsidiary of Merck & Co., Inc., the manufacturer of sitagliptin. **R.D.L**. reports receiving research grants from Bristol-Myers Squibb and GlaxoSmithKline and serving as a consultant for Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Merck, Pfizer, and Portola. **D.K.M.** has received personal fees from Boehringer-Ingelheim, Janssen Research and Development LLC, Sanofi-Aventis Group, Merck Sharp and Dohme, Daiichi Sankyo, Inc., Lilly USA, Novo Nordisk, GlaxoSmithKline, Takeda Pharmaceuticals North America, AstraZeneca, Lexicon, Regeneron, University of Oxford, Duke Clinical Research Institute, Partners Healthcare, and the Cleveland Clinic Foundation. **H.W.R.** conducts clinical trials, lectures, and serves on advisory boards for AstraZeneca, Boehringer-Ingelheim,, Janssen, Lilly, Merck, Novo Nordisk, Sanofi and Regeneron. **I.S.** has received grants, personal fees and support from Merck, AstraZeneca, Janssen, Boehringer-Ingelheim, Novartis, Novo Nordisk, Glaxo SmithKline and Servier. **T.T.** has received lecture fees and serves on advisory boards for Merck, Boehringer-

Ingelheim, Novo Nordisk, Sanofi, Eli Lilly, Novartis, Servier, AstraZeneca. **J.W.** reports serving as a consultant for AstraZeneca, Novo-Nordisk, E. Lilly, Novartis, Boehringer-Ingelheim, Sanofi. **E.D.P**. has received grants and personal fees from Janssen, grants from Eli Lilly, and personal fees from AstraZeneca, Bayer, and Sanofi. R.R.H. has received grants and personal fees from Merck, grants from Bayer, and AstraZeneca, personal fees from Amgen, Bayer, Intarcia, Novartis, Novo Nordisk, and other support from GlaxoSmithKline, Janssen, and Takeda. **R.R.H.** has received grants and personal fees from Merck, grants from Bayer, and AstraZeneca, personal fees from Amgen, Bayer, Intarcia, Novartis, Novo Nordisk, and other support from GlaxoSmithKline, Janssen, and Takeda. The other authors report no potential conflicts of interest.

Author contributions: J.H.C and W.A.B. and drafted and edited the manuscript. R.R.H. drafted and edited the manuscript and contributed to the study design, data analysis and interpretation. S.R.S. performed the statistical analyses and edited the manuscript. G.L.B., M.A., L.-M.C., T.T., R.D.L., A.R., H.W.R., I.S., and J.W. edited the manuscript. S.S.E., D.K.M., and E.D.P. edited the manuscript and contributed to the study design, data analysis and interpretation.

Previous presentations. Parts of this work were presented at the American Diabetes Association, European Association for the Study of Diabetes, and International Diabetes Federation annual meetings in 2015.

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Figure Legend

Figure 1. (A) Estimated glomerular filtration rate (eGFR) over 4 years (N=13,604). (B) Urinary albumin-to-creatinine ratio (UACR) over 4 years (N=3,832). Data are plotted at each visit as mean (±1 SD) for eGFR and median (25th, 75th percentile) for UACR among patients with the measurement at the visit. Patients without baseline and at least one post-baseline measure are not shown at any visit.

Table 1—Association of cardiovascular endpoints with baseline eGFR stages

Endpoint	Total number of events (events *per* 100 patient-years)				Adjusted hazard ratio (95% confidence interval) *vs.* eGFR ≥90 ml/min/1.73m²			
	Stage 1 eGFR ≥90 ml/min/1.73m²	Stage 2 eGFR 60-89 ml/min/1.73m²	Stage 3a eGFR 45-59 ml/min/1.73m²	Stage 3b eGFR 30-44 ml/min/1.73m²	Stage 2 eGFR 60-89 ml/min/1.73m²	Stage 3a eGFR 45-59 ml/min/1.73m²	Stage 3b eGFR 30-44 ml/min/1.73m²	*P* value
CV death, MI, stroke, or hospitalization for UA	330 (3.52)	799 (3.55)	393 (5.74)	145 (7.34)	0.93 (0.82–1.06)	1.28 (1.10–1.49)	1.39 (1.13–1.72)	<0.0001
CV death, MI, or stroke	281 (2.97)	692 (3.05)	358 (5.17)	141 (7.11)	0.94 (0.82–1.09)	1.36 (1.15–1.61)	1.60 (1.29–1.99)	<0.0001
CV death	136 (1.37)	333 (1.39)	188 (2.52)	79 (3.65)	0.89 (0.73–1.09)	1.31 (1.04–1.65)	1.65 (1.22–2.23)	<0.0001
Hospitalization for unstable angina	57 (0.59)	135 (0.58)	42 (0.59)	7 (0.33)	0.95 (0.69–1.31)	0.85 (0.56–1.30)	0.40 (0.18–0.91)	0.17
MI	130 (1.36)	281 (1.22)	141 (2.00)	57 (2.81)	0.86 (0.69–1.06)	1.26 (0.98–1.63)	1.50 (1.07–2.11)	0.0001
Stroke	53 (0.55)	185 (0.80)	92 (1.29)	27 (1.30)	1.37 (1.00–1.86)	1.96 (1.37–2.79)	1.79 (1.10–2.93)	0.0016
All cause death	186 (1.87)	489 (2.04)	267 (3.57)	130 (6.01)	0.94 (0.79–1.12)	1.35 (1.11–1.64)	1.97 (1.55–2.52)	<0.0001
Hospitalization for heart failure	62 (0.64)	214 (0.92)	107 (1.50)	68 (3.36)	1.17 (0.88–1.56)	1.50 (1.08–2.08)	2.64 (1.82–3.83)	<0.0001

Table 2—Association of cardiovascular endpoints with baseline UACR categories

Endpoint	Total number of events (events *per* 100 patient-years)			Adjusted hazard ratio (95% confidence interval) *vs.* Normoalbuminuria (UACR<30 mg/g)		
	Normoalbuminuria UACR<30 mg/g	Microalbuminuria UACR 30-300 mg/g	Macroalbuminuria UACR>300 mg/g	UACR 30-300 mg/g	UACR>300 mg/g	*P* value
CV death, MI, stroke, or hospitalization for UA	381 (3.54)	165 (5.03)	46 (7.13)	1.19 (0.99–1.43)	1.33 (0.96–1.83)	0.0797
CV death, MI, or stroke	331 (3.05)	155 (4.71)	46 (7.13)	1.28 (1.05–1.56)	1.52 (1.10–2.11)	0.0066
CV death	119 (1.03)	79 (2.26)	24 (3.41)	1.86 (1.39–2.49)	2.27 (1.43–3.60)	<0.0001
Hospitalization for unstable angina	65 (0.58)	12 (0.35)	0 (0)	0.56 (0.30–1.06)	-	0.2018
MI	174 (1.58)	63 (1.88)	22 (3.36)	1.04 (0.77–1.40)	1.52 (0.95–2.42)	0.2172
Stroke	79 (0.71)	35 (1.03)	12 (1.78)	1.16 (0.77–1.75)	1.75 (0.92–3.32)	0.2179
All-cause death	203 (1.76)	105 (3)	34 (4.83)	1.45 (1.14–1.84)	1.82 (1.25–2.66)	0.0006
Hospitalization for heart failure	94 (0.84)	53 (1.57)	20 (3.07)	1.63 (1.15–2.29)	2.78 (1.68–4.59)	<0.0001

Table 3—Estimated mean 4-year eGFR and UACR between treatment group differences (sitagliptin minus placebo), overall and by baseline eGFR stages

	Baseline value	Mean between-group treatment difference (95% CI)[†]	*P* value[†]
eGFR (N=13,604), ml/min/1.73m²			
Overall	75.1±21.0	-1.34 (-1.76 to -0.91)	<0.0001
Stage 1 (eGFR ≥90 ml/min/1.73m²)	104±14	-0.22 (-1.19 to 0.75)	Interaction p=0.14
Stage 2 (eGFR 60-89 ml/min/1.73m²)	73±9	-1.42 (-2.05 to -0.79)	
Stage 3a (eGFR 45-59 ml/min/1.73m²)	53±4	-1.33 (-2.45 to -0.21)	
Stage 3b (eGFR 30-44 ml/min/1.73m²)	39±4	-2.25 (-4.27 to -0.23)	
UACR (N=3,832), mg/g			
Overall	11.1 (3.9, 35.0)	-0.18 (-0.35 to -0.02)	0.031
Stage 1 (eGFR ≥90 ml/min/1.73m²)	11.0 (4.7, 30.2)	-0.18 (-0.53 to 0.16)	Interaction p=0.68
Stage 2 (eGFR 60-89 ml/min/1.73m²)	9.7 (3.5, 29.2)	-0.20 (-0.42 to 0.02)	
Stage 3a (eGFR 45-59 ml/min/1.73m²)	14.3 (4.1, 55.4)	-0.30 (-0.70 to 0.09)	
Stage 3b (eGFR 30-44 ml/min/1.73m²)	27.7 (9.7, 126.6)	0.23 (-0.54 to 1.00)	

eGFR data are presented as mean ± 1SD. UACR data are presented as median (25^{th}, 75^{th} percentiles).

[†] The estimated mean difference and P value are derived from repeated measures over the 4-year time frame. Estimated mean differences for UACR are modeled and presented with a Box-Cox transformation.

Models include region, baseline eGFR stage, time of measure, treatment, and the eGFR stage-by-treatment interaction. The UACR analysis also adjusts for continuous baseline UACR.